Reviewer’s report

Title: Venous endothelial injury in central nervous system diseases

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Reviewer: Gediminas Cepinskas

Reviewer’s report:

The manuscript (a review article) by J. Steven Alexander et al. entitled “Venous endothelial injury in central nervous system diseases” is presented for review.

In this manuscript the authors present a comprehensive review on the potential mechanisms (e.g. the role of venous dysfunction) associated to the development/progression of the most devastating inflammatory demyelinating diseases of CNS (e.g MS, acute disseminated encephalomyelitis, etc).

It is this reviewer’s opinion that the manuscript is very well-written and elegantly highlights the newest findings (e.g. the potentially critical role of venous endothelium in the initiation/propagation of the inflammatory demyelinating diseases) in the field. The authors present the mechanistic insights/signaling specifically relevant to the venous endothelial cell physiology/pathophysiology and compare (where appropriate) venous endothelial responses to the ones observed in arterial endothelium. In a light of a limited work addressing the pathophysiology (at the levels of both, anatomical and functional abnormalities) of cerebral venous endothelium this review is very timely and necessary in order to further the active research in this field.

With this in mind there are no major concerns with the manuscript.

Minor concerns:

1) It would be helpful to the reader if a diagram depicting the key molecular/structural differences between venous and arterial endothelium would be presented.
2) There are some inaccuracies (e.g. missing or misspelled words) in the text:
   a) p4. (second last paragraph: “Interestingly, have shown…”. Missing word(s)).
   b) p5. (1st paragraph) “…anti-protease” (misspelled)
   c) p5. (3rd paragraph, second sentence: “We have previously reported…”). Please indicate which cells have been used.
   d) p6. (3rd paragraph. The sentence: “Importantly, Takase et al show…” needs to be clarified.
   e) p8. (1st paragraph, second sentence: “Integrin alpha9…”). Finish the sentence please.
   f) p8. (3rd paragraph, second sentence: “Inflammatory demyelination…”). Please correct/clarify the sentence.
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests